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(54) Title: EXTENDED-RELEASE FORM OF DILTIAZEM

(57) Abstract

An extended-release galenical form of Diltiazem or a pharmaceutically acceptable salt thereof, which comprises beads containing said Diltiazem or a pharmaceutically acceptable salt thereof as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

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EXTENDED RELEASE FORM OF DILTIAZEM

FIELD OF INVENTION

The present invention relates to an extended release form of Diltiazem, a process for the manufacture thereof and pharmaceutical compositions containing the same.

BACKGROUND OF THE INVENTION

Diltiazem hydrochloride is used in medicine principally for its calcium channel blocking properties, and, therefore, finds application in the treatment of angina pectoris and hypertension, either alone or in combination with other medications.

Although the mechanism for calcium channel blocking is not completely understood, calcium ion entry is believed to be inhibited through select voltage, with the sensitive areas termed "slow channels", across cell membranes. By reducing intracellular calcium concentration in cardiac and vascular smooth muscle cells, coronary arteries, peripheral arteries and arterioles are dilated and heart rate may be reduced. Also, myocardial contractibility may be decreased and atrioventricular nodal conduction may be slowed. The activity of diltiazem in humans is directly related to its blood or plasma concentration.

For illnesses which require continuous and constant control, such as hypertension and angina pectoris, Diltiazem must be administered every 6 to 8 hours, as it has a very short half-life in blood of only about 3 to 4 hours. However, such frequent administration times render the treatment very annoying or even impossible to effect, particularly during the night. Further, after each administration of an immediate-release galenic form of Diltiazem, which generally is necessary four times per day, a succession of rapidly increasing and decreasing plasmatic Diltiazem concentrations are established. Thus, the organism being treated and the target organ, more particularly the heart, are alternatively subjected to overdoses and to underdoses of medicine.

In order to alleviate these drawbacks, a first galenic form of sustained-release Diltiazem known under the

trade name CARDIZEM SR® was developed and presented in the form of "erodible pellets", U.S. Patent 4,721,619. Although this form affords a reduction in peak concentration and in the number of daily intakes from 4 to 2, it does not eliminate high Diltiazem blood concentration between successive medication intakes. Hence, the patient is still obliged to take the medication twice daily. The products as described in U.S. 4,721,619 are prepared by a building up process which requires, as described therein, between 50 and 200 layers so as to obtain a core which, thereafter, requires between 20 and 40 layers of coating so as to obtain the membrane. Moreover, the solvent of the polymer solution used to make the membrane is constituted by organic solvents, such as isopropanol, methanol, acetone, and methylene chloride, which are dangerous to use due to their flammability and/or toxicity. Such solvents are also environmentally hazardous. Particular care must be taken to avoid any traces of solvent in the final product because these solvents are toxic and are unsuitable in the product which is administered orally.

Thus, a need continues to exist for a multiple unit extended-release diltiazem hydrochloride galenical form which need be administered only once daily, and from which blood Diltiazem concentrations are not effected by the concomitant intake of food, and, further, which can be made by a process not using organic solvents.

SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide galenic forms of Diltiazem with extended release of the active substance.

It is also an object of this invention to provide galenic forms of Diltiazem having excellent bioavailability while avoiding plasmatic concentration peaks.

The above objects and others which will become more apparent in view of the following disclosure are provided by an extended-release galenical form of a pharmaceutically acceptable salt of Diltiazem, which

comprises beads containing the pharmaceutically acceptable salt of Diltiazem as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

Thus, according to one embodiment of the invention an extended-release galenical composition comprises beads comprising:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein said wetting agent comprises a sugar, C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of an aqueous dispersion of a water-soluble or water-dispersible polymer or copolymer, for example a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant.

According to another embodiment a pharmaceutical composition is provided, comprising in capsule form an effective amount of one or more pharmaceutically acceptable salts of Diltiazem, and a wetting agent, wherein said wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a

pharmaceutically acceptable adjuvant, and one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

According to another aspect of the invention a method of treating angina pectoris or hypertension or both in a mammal is provided which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof and a wetting agent in the form of beads, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein the beads are coated with a microporous membrane of for example an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant.

According to another aspect of the invention, the extended-release galenical formulation is adapted to release Diltiazem in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate in the order of:

between about 5% and about 20% after 2 hours, for example 9% after two hours (in one embodiment with 5% after 1 hour);

between about 20% and about 50% after four hours, for example 33-34% after four hours;

between about 30% and about 70% after six hours, for example 54% after 6 hours; and

between about 50% and about 90% after 8 hours, for example, between about 62% and about 82% after 8 hours.

Thus, according to another aspect of the invention an extended-release galenical composition is provided comprising beads containing:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of for example an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate on the order of:

9% after 2 hours,
33% after 4 hours,
54% after 6 hours, and
between 62% and 83% after 8 hours.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be illustrated with respect to the following drawings illustrating embodiments of the invention in which:

Figure 1 illustrates the effect of the present invention in gradually releasing Diltiazem in a relatively uniform manner over a period of about one day after the 8th once daily administration in comparison with the effect of a conventional product after the 8th day of administration twice daily.

Figure 2 illustrates in the solid curve, the mean plasma levels obtained when the product of the present invention is taken without food. The dotted curve represents mean plasma levels obtained when the product is taken with food.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS OF THE INVENTION

Diltiazem or (2S-cis)-3-(Acetyloxy)-5-[2-(dimethyl-amino)ethyl]-2,3-dihydro-2, (4-methoxyphenyl)-1,5-benzothiazepin-4(5H) has been known for more that 20 years. The synthesis thereof is described in German patent 1,805,714, corresponding to U.S. patent 3,562,257.

The present invention relates to novel galenic forms of Diltiazem being characterized by having an extended-release of the active substance. These galenic forms afford excellent bioavailability while avoiding plasmatic concentration peaks, so that it is now possible to maintain diltiazem plasmatic concentration in a desired, effective range while simplifying the administration of the medicine to only once daily.

According to the present invention, the Diltiazem extended-release galenic forms are substantially characterized by the fact that they are constituted by beads containing a pharmaceutically acceptable salt of Diltiazem as an active substance, associated with at least a wetting agent, the beads being covered with a microporous membrane constituted by at least a water-soluble or water-dispersible polymer or copolymer such as a copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, and a pharmacologically acceptable adjuvant.

In accordance with the present invention, any pharmaceutically acceptable salt of Diltiazem may be prepared in extended release form. For example, such salts may include the hydrochloride, sulfate or phosphate salts. However, they may also include the acetate, citrate or lactate salts, for example. It is preferred, however, that the hydrochloride salt be used.

In more detail, the microporous membrane, whereof the Diltiazem-containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer, including at least one adjuvant which may be the active substance. These galenic forms afford

excellent bioavailability while avoiding plasmatic concentrations peaks, so that it is now possible to maintain diltiazem plasmatic concentrations in a desired, effective range while simplifying the administration of the medicine to only once daily.

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In more detail, the microporous membrane, whereof the Diltiazem-containing microgranules are covered, is constituted by a mixture of a water-soluble and/or water-dispersible copolymer, including at least one adjuvant which may be plastifying agents, pigments, fillers, wetting agent lubricants and antifoam agents.

The active substance-containing beads are presented in form of spherules the diameter of which is between about 0.05 mm and 3 mm, preferably between about 0.1 mm and 2 mm.

Among the wetting agents associated with the Diltiazem or salt thereof in the beads, the following compounds may more particularly be exemplified:

sugars, for example saccharose, mannitol, sorbitol and lactose;

lecithins;

C_{12} to C_{20} fatty acid esters of saccharose, commercialized under the name of sucroesters (Gattefosse, France) or under the name of crodesters (Croda, U.K.);

xylose esters or xylites;

polyoxyethylenic glycerides;

esters of fatty acids and polyoxyethylene (Brijs, Renex and Eumulgines, Henkel, RFA);

sorbitan fatty acid esters (Span, Atlas, U.S.A.);

polyglycides-glycerides and polyglycides-alcohols esters (Gelucires, Gattefosse, France).

In addition to at least one of the above-named wetting agents, the beads may contain excipients or carriers, such as:

Microcrystalline celluloses, such as Avicel products (FMC, U.S.A.); methylcelluloses, carboxymethylcelluloses, hydroxyethylcelluloses (Natrosol, Hercules, U.S.A.), hydroxypropyl celluloses (Klucels, Hercules, U.S.A.); and starches.

Among the water-soluble and/or dispersible film-forming polymers or copolymers constituting the microporous membrane, may be mentioned particularly polyacrylates and polymethacrylates of the Eudragit type, such as Eudragit E30D, L30D, RS - 30 D of Röhm Pharm (RFA), ethylcelluloses, such as Ethocels of DOW, U.S.A. and such as AquaCoat of FMC, U.S.A., Hydroxypropyl cellulose and hydroxypropyl-methylcellulose and their derivations.

These polymers or copolymers may be associated into the microporous membrane with at least one adjuvant as exemplified by the following:

plastifying agents, such as triacetin, dibutylphthalate, dibutylsebacate, citric acid esters, polyethyleneglycols, polypropyleneglycols and polyvinylpyrrolidone;

pigments, such as iron oxides and titanium oxide;

fillers, such as lactose and sucrose;

wetting agents, such as surfactive agents of the Span and Tween types, namely partial esters of fatty acids (lauric, palmitic, stearic and oleic acids) and anhydrides of hexitols derived from sorbitol possibly containing polyoxyethylenic chains, preferably surfactive agents of the Tween type, namely Tween 80, as well as polyethyleneglycols;

lubricants, such as magnesium stearate and talc;

antifoaming agents, such as silicone oil.

In addition to the polymer or copolymer, the microporous membrane contains, preferably, talc and/or magnesium stearate as a lubricant, polyvinylpyrrolidone as a plastifying agent, titanium dioxide as a pigment, Tween 80 as an emulsifier, and silicone oil as an antifoaming agent.

Generally, the thickness of the microporous membrane is expressed by the percentage of the coating applied to the uncoated beads.

The weight of the microporous membranes may be 2 to 35%, preferably, 5 to 22%, of the weight of said microgranules. These beads may contain the Diltiazem salt in an amount of 20 to 95% by weight, preferably 30 to 85% by weight. The microporous membrane may contain 5 to 95% and, preferably, 30 to 90% of polymers, polymer mixture or copolymers.

The invention relates also to a medicine containing Diltiazem or salt thereof for extended release, the medicine being constituted by beads containing the Diltiazem or salt, such as the hydrochloride, and at least a wetting agent, coated with at least one polymer-based microporous membrane, the coated beads being contained in capsules, little bags or dosage dispensers.

The present invention relates also to a process for obtaining novel forms of a Diltiazem or salt thereof having extended-release in the gastro-intestinal tractus, said process entailing preparing beads and coating the same with a single microporous membrane.

The beads of the Diltiazem or salt thereof may be prepared using a conventional technique. A first technique consists in mixing the Diltiazem or salt thereof with the wetting agent(s) in a melted or finely divided form, or in solution, in the presence of a solvent, such as water, so as to obtain an extrudable paste or plastic mass. Said paste is thereafter extruded in an extruder and then rendered spherical. Several extruder types are usable, for example the extruder for ALEXANDER WERK (RFA) or the apparatus called X-truder of FUJI-PAUDAL (Japan). For obtaining microspheres or beads from the extruded product provided in the form of spaghetti, an apparatus called "spheronizer" (CALEVA Great-Britain) or MARUMERIZER (FUJIU-PAUDAL Japan) type is used.

Another conventional technique for obtaining beads consists in spraying and/or dusting cores obtained through agglomeration of the Diltiazem or salt thereof, such as the chlorohydrate, contingently mixed to at least a wetting agent, with a dispersion or solution of at least one wetting agent, for example in a known pilling turbine or in a granulating apparatus, such as the CF granulator system of FREUND INDUSTRIAL CO. (Japan), or in a known planetary granulator such as the collette (Belgium) type.

The obtained beads are dried by any means, for example in an oven or by means of a gas in a fluidized bed.

Finally, said beads are calibrated to the necessary diameter by passage through appropriate screens.

A pasty or plastic mixture, appropriate to be granulated by means of any one of the above described techniques, may contain the following weight proportions of the Diltiazem or salt thereof, wetting agents and carriers or excipients:

20 to 85%; Diltiazem hydrochloride

2 to 20% sucroesters WE 15 (wetting agent);

5 to 25% Avicel PH 101 (microcrystalline cellulose of FMC, U.S.A.);

2 TO 10% Methocel E 5 (hydroxypropyl-

methylcellulose of DOW, U.S.A.);
1 to 15% polyvinylpyrrolidone and
5 to 40% distilled water.

Said microporous membrane may be applied onto said beads by pulverizing an aqueous solution or dispersion of at least one of the above-named polymers and at least one of the above-mentioned adjuvants onto said beads. This pulverization may be carried out by spray-gunning or by pulverizing the above-named dispersion into a turbine or fluidized bed.

Generally, the present extended release form composition of Diltiazem salt is administered orally. The dosage amount is subject to the response of the individual patient; however, in general, from about 120 mg to about 480 mg per day of Diltiazem salt is administered per day per patient in total.

Additionally, the extended release form composition of the present invention may include other pharmaceutically active ingredients than the Diltiazem salt, provided that the other active ingredient is not pharmaceutically incompatible with the Diltiazem salt.

For example, other pharmaceutically active ingredients, such as β-adrenoceptor blocking agents or diuretics may be used in the present compositions. However, these are only examples and are not intended to be limitative.

As examples of β-adrenoceptor blocking agents, drugs such as Propranolol, Atenolol, Labetalol, Prindolol or Sotalol may be used, for example.

As examples of diuretic agents, drugs such as Hydrochlorothiazide, Furosemide, Ethacrynic Acid or Chlorothiazide may be used, for example.

Further, the additional associated drugs may be present in extended-release form also, if desired; however, they need not be.

The present invention will now be further illustrated by reference to certain examples which are

provided solely for purposes of illustration and are not intended to be limitative.

According to an illustrative embodiment of the present invention, said microporous membrane may be obtained, starting from an aqueous dispersion which contains by weight:

10 to 70 Eudragit E30D (polymer)
0.5 to 15% talc (lubricant)
0.5 to 15% Titanium dioxide (lubricant)
0.5 to 15% Magnesium stearate (lubricant)
0.5 to 15% polyvinylpyrrolidone (plastifying agent)
0.01 to 2% silicone oil (antifoaming agent);
0.05 to 5% polysorbate 80 (wetting agent)
10 to 70% water (carrier)

EXAMPLES

The present invention will now be further illustrated by reference to certain examples, which are provided solely for purposes of illustration and are not intended to be limitative. In particular, examples are provided for Diltiazem Hydrochloride extended-release galenic forms, a process for preparing the same, therapeutic applications thereof and pharmacokinetic controls using the present galenic forms.

Example 1 - beads manufacture

Diltiazem hydrochloride	1120 g
Lactose	119 g
Microcrystalline cellulose (Avicel pH 101)	140 g
Povidone K. 30	21 g

After introducing the powders into a planetary mixer and granulating with water, the obtained plastic mass is extruded through a cylinder with 1 mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to

obtain beads, by means of a spheronizer. After drying at 60°C for 12 hours, the beads are sifted and the fraction with size comprised between 0.7 mm and 1.4 mm are retained. 1,179 g of beads were obtained yield (84%).

Example 2

Diltiazem Hydrochloride	560 g
Crodesta F 160	59.5 g
Microcrystalline cellulose (Avicel pH 101)	70 g
Povidone K 30	10.5 g

The ingredients are introduced in a planetary mixer and dry mixed for approximately 15 minutes. Thereafter, 100 ml water USP is added and the mixing is pursued for 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal extruder equipped with a 1 mm screen so as to obtain "spaghetties". A spheronizer type caleva is used so as to transform the extruded product into beads. After drying for 12 hours on trays in an oven at 60°C, the beads are sieved so as to eliminate the ones with a size larger than 1.4 mm and with a size smaller that 0.7 mm.

The amount of beads obtained with size comprised between 0.7 mm and 1.4 mm was 639.1 g (yield 91.3%).

Example 3

Beads prepared in Example 1 were coated in a STREA-1 (Aeromatic) fluidized bed using the "Top spraying" technique. 440 g of coating suspension of the following composition was applied on 500 g of beads. Thereafter, the coated beads were dried at 50°C during 16 hours.

Coating suspension composition:	
Magnesium stearate	12.5 g
Titanium dioxide	5.0 g
Povidone k 30	5.0 g
Eudragit NE30D	620.0 g
Talc USP	17.5 g
water	338.0 g
Simethicone	1.0 g
Tween 80	0.8 g

"In vitro" dissolutions were obtained using the apparatus #2 as described in the United States Pharmacopeia. The 900 ml dissolution medium consisted of a phosphate butter of 5.8 pH and a revolution speed of 100 rpm.

elapsed time [h]	percent dissolved [%]
1	5
4	34
8	62
12	84

Example 4

The beads, as in Example 2, were coated using a fluidized bed coater equipped with "wurster" system. 8 kg of uncoated beads were introduced in an Aeromatic Aerocoater and 2.77 kg of the following coating suspension was applied at a rate of 30 - 35 g per minute. Thereafter, the coated beads were dried for 15 hours at 45°C.

Coating suspension:		
Magnesium stearate	0.636	kg
Talc	0.636	kg
Titanium dioxide	0.0909	kg
Hydroxypropylmethylcellulose	0.200	kg
Polysorbate 80 NF	0.007	kg
Simethicone c emulsion	0.018	kg

Eudragit NE 30 D	12.4	kg
purified water	6.7	kg

Dissolution "in vitro"

The results were obtained using the same equipment as in Example 3. The dissolution medium was composed of 900 ml of water and the temperature was maintained at 37 ± 0.5°C

elapsed time [h]	percent dissolved [%]
2	9
4	33
6	54
8	82

Pharmacokinetical results

The new galenic form of Example 4 was the object of a pharmacokinetical study in comparison with a form in accordance to the prior art as described in U.S. Patent 4,721,619 (Cardizen SR®). Therefore, 6 healthy subjects received successively in a random order 300 mg of each of the 2 products. The product of Example 4 was administered at a dose of 300 mg once daily, while the product on the market was administered twice daily at a dose of 150 mg (300 mg daily total dose) for 7 days. On each of the eight days, 11 samples of blood were withdrawn when the product of Example 4 was administered and 15 blood samples were withdrawn after the Cardizen SR® administration. Diltiazem plasma levels were assayed using a specific high pressure liquid chromatographic method. Figure 1 shows the results obtained: the continuous line represents the Diltiazem plasma levels obtained with the product of Example 4 and the broken line, the Diltiazem plasma levels of Cardizen SR®.

Figure 1

Pharmacokinetical parameters:

	Units	Example 4	Cardizen SR®
Area under the curve [0-24h]	mg.h/ml	2782 ± 1037	2864 ± 1222
Maximal concentration	mg/ml	116.3 ± 54.1	192.7 ± 85.3
Time of maximum concentration	h	8.0 ± 1.8	5.2 ± 2.8
Fluctuation	%	85.7 ± 25.7	109.5 ± 25
Time during the concentration is above 75% of the maximum concentration	h	9.8 ± 2.3	6.7 ± 3.7

From these results, the following conclusion can be drawn:

Firstly, Fig. 1 shows that the Diltiazem plasma levels obtained after a once daily administration of one of the products of the present invention are comparable to the ones obtained after a twice daily administration of the product of the previous art.

Secondly, the bioavailability expressed by the areas under the curve of the 2 products is equivalent (no statistical detectable difference).

Thirdly, the maximal concentration and the fluctuations obtained after a once daily administration of the product of the present invention is lower than the one obtained with Cardizen SR® after a twice daily administration.

Fourthly, the time that the concentration is above 75% of the maximum concentration is 46% longer after the once daily administration of the product of the present invention than with the product of the previous art when given twice daily.

Food effect study

The product of Example 4 was given to 24 healthy volunteers and the bioavailability was measured after a single oral dose of 300 mg given with and without food.

The clinical trial was conducted as an open, single dose, randomized, cross-over study. Blood samples were obtained before and up until 36 hours after the administration. The experiment was repeated in the same subjects with the other treatment during an interval of 7 days. The plasma concentration of Diltiazem was determined in all available samples using an HPLC method. Pharmacokinetics parameters were derived from the individual plasma concentration versus time profiles and statistically compared for treatment differences and assessment of bioequivalence. Figure 2 curves show the mean plasma levels obtained when the product is taken without food and the dotted curve, the mean plasma levels obtained when the product is taken with food.

Figure 2

Pharmacokinetics parameter - product of Example 4

	Units	Fasting	Food
Area under the curve (total)	mg.h/ml	1988 ± 119	1925 ± 109
Mean residence time	h	21.3 ± 0.7	19.9 ± 0.9
K_a	h^{-1}	0.283 + 0.024	0.300 + 0.027
Maximum concentration	mg/ml	100 ± 4.8	112 ± 5.9

No statistical difference was detectable. The product of Example 4 given with food is bioequivalent to the administration without food to within less than 20%, regarding the area under the curve, mean residence time and maximum concentration. The larger interval obtained for K_a

was due to the higher variability of this parameter, the difference between the treatment means remaining small (6.%).

From all the results, it appears clearly that the product of the present invention can be administered once a day and that the plasma concentration variations are lower than the ones obtained with the conventional product given twice a day.

Having described the present invention, it will now be apparent to one skilled in the art that many changes and modifications may be made to the above-described embodiments while remaining within the spirit and the scope of the present invention.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE AS FOLLOWS:

1. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing an effective amount of said one or more Diltiazem salts as an active ingredient and a wetting agent, said beads being coated with a microporous membrane comprising at least a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

2. The extended-release galenical composition of Claim 1, wherein said salt is the hydrochloride salt.

3. The extended-release galenical composition of Claim 1, wherein said water-soluble or water-dispersible polymer is a polymer of acrylic acid methyl ester and acrylic acid ethyl ester or a copolymer of both.

4. The extended-release galenical composition of Claim 1, wherein said wetting agent comprises a sugar, C_{12} to C_{20} fatty acid esters of sucrose or xylose, glycerides of sucrose, fatty acid esters of polyoxyethylene, ethers of fatty alcohols and polyoxyethylene, esters of sorbitan, esters of polyoxyethylene sorbitan, glyceride-polyglycides, alcohol-polyglycide esters or lecithins or any combination thereof.

5. The extended-release galenical composition of Claim 1, wherein the weight of the microporous membrane is about 4 to 35% by wt. of that of the uncoated beads.

6. A pharmaceutical composition containing an extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises:

a) beads containing an effective amount of one or more pharmaceutically acceptable salts of Diltiazem and a wetting agent, said beads being coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant, and

b) one or more other pharmaceutically active ingredients which pharmaceutically active ingredients are pharmaceutically compatible with said one or more Diltiazem salts.

7. The pharmaceutical composition of Claim 6, wherein said one or more other pharmaceutically active ingredients comprises β-adrenoceptor or diuretic compounds or compositions containing the same.

8. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof in the form of beads, said beads being coated with a microporous membrane containing at least a water-soluble or water-dispersible polymer or copolymer, and a pharmaceutically acceptable adjuvant.

9. The method of Claim 8, wherein said administration is orally and once per day.

10. The method of Claim 8, wherein said mammal is a human.

11. The method of Claim 9, wherein from about 120 mg to about 480 mg of said one or more Diltiazem salts in total are administered per day.

12. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads, said beads comprising:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein said wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane of at least a water-soluble or water-dispersible polymer or copolymer and a pharmaceutically acceptable adjuvant.

13. The extended-release galenical composition of Claim 12, wherein said salt is the hydrochloride salt.

14. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

15. The extended-release galenical composition of Claim 12, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

16. The extended-release galenical composition of Claim 12, wherein the water-soluble or water-dispersible polymer or copolymer comprises an aqueous dispersion or a neutral copolymer or ethyl acrylate and methyl methacrylate.

17. A pharmaceutical composition comprising an extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which

comprises in capsule form,

beads comprising an effective amount of one or more pharmaceutically-acceptable salts of Diltiazem, and a wetting agent, wherein said wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, and

one or more other pharmaceutically active ingredients which are pharmaceutically compatible with said one or more Diltiazem salts.

18. The pharmaceutical composition of Claim 17, wherein said one or more other pharmaceutically active ingredients comprises β-adrenoceptor or diuretic compounds or compositions containing the same.

19. The pharmaceutical composition of Claim 17, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

20. The pharmaceutical composition of Claim 17, wherein said salt is the hydrochloride salt.

21. The pharmaceutical composition of Claim 17, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

22. A method for treating angina pectoris or hypertension or both in a mammal, which comprises administering to said mammal an effective amount of an

extended-release galenical composition of Diltiazem or a pharmaceutically acceptable salt thereof in the form of beads and a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, an alcohol-polyglycide ester or lecithins or any combination thereof, wherein the beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant.

23. The method of Claim 22, wherein said administration is orally and once per day.

24. The method of Claim 22, wherein said mammal is a human.

25. The method of Claim 23, wherein from about 120 mg to about 480 mg of said one of more Diltiazem salts are administered in total per day.

26. The method of Claim 22, wherein said salt is the hydrochloride salt.

27. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of

polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof, wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically-acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no. 2 is used at 100 rpm, at a rate on the order of:

9% after 2 hours,
33% after 4 hours,
54% after 6 hours, and
between 62% and 82% after 8 hours.

28. The extended-release galenical composition of Claim 27, wherein said salt is the hydrochloride salt.

29. The extended-release galenical composition of Claim 27, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

30. The extended-release galenical composition of Claim 29, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

31. An extended-release galenical composition of one or more pharmaceutically acceptable salts of Diltiazem, which comprises beads containing:

a) an effective amount of said one or more Diltiazem salts as an active ingredient, and

b) a wetting agent, wherein the wetting agent comprises a sugar, a C_{12}-C_{20} fatty acid ester of sucrose or xylose, a glyceride of sucrose, a fatty acid ester of polyoxyethylene, an ether of fatty alcohols and polyoxyethylene, an ester of sorbitan, an ester of polyoxyethylene sorbitan, a glyceride-polyglycide, alcohol-polyglycide ester or lecithins or any combination thereof,

wherein said beads are coated with a microporous membrane constituted by an aqueous dispersion of a neutral copolymer of ethyl acrylate and methyl methacrylate, and a pharmaceutically acceptable adjuvant, wherein the membrane is adapted to release Diltiazem, in 900 ml of water when USP XXII, apparatus no 2. is used at 100 rpm, at a rate on the order of:

between 5% and 20% after 2 hours,
between 20% and 50% after 4 hours,
between 30% and 70% after 6 hours, and
between 50% and 90% after 8 hours.

32. The extended-release galenical composition of Claim 31, wherein said salt is the hydrochloride salt.

33. The extended-release galenical composition of Claim 31, wherein the weight of the microporous membrane is about 2 to 35% by weight of that of the uncoated beads.

34. The extended-release galenical composition of Claim 33, wherein the weight of the microporous membrane is about 5 to 22% by weight of that of the uncoated beads.

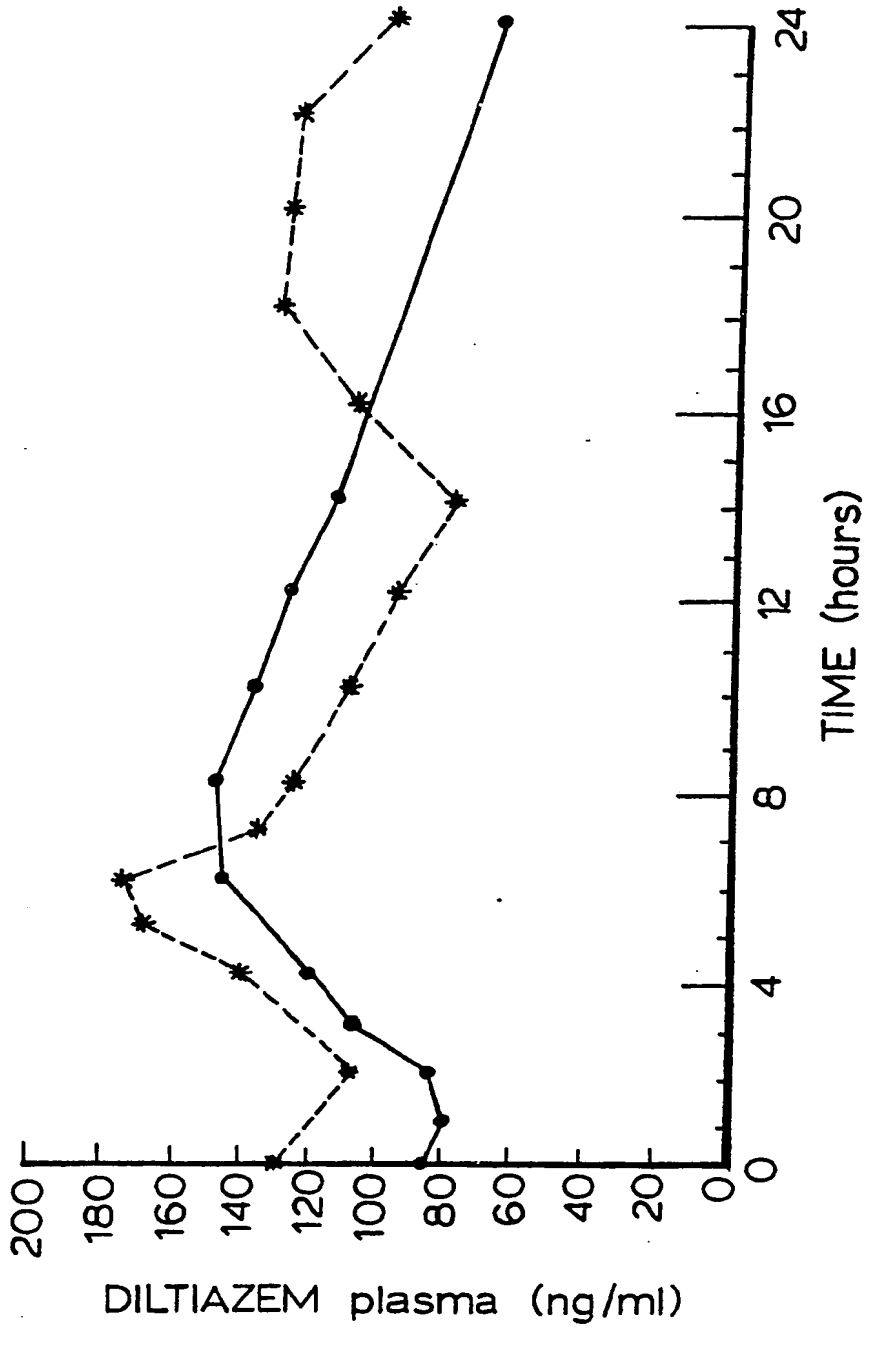

FIG.1.

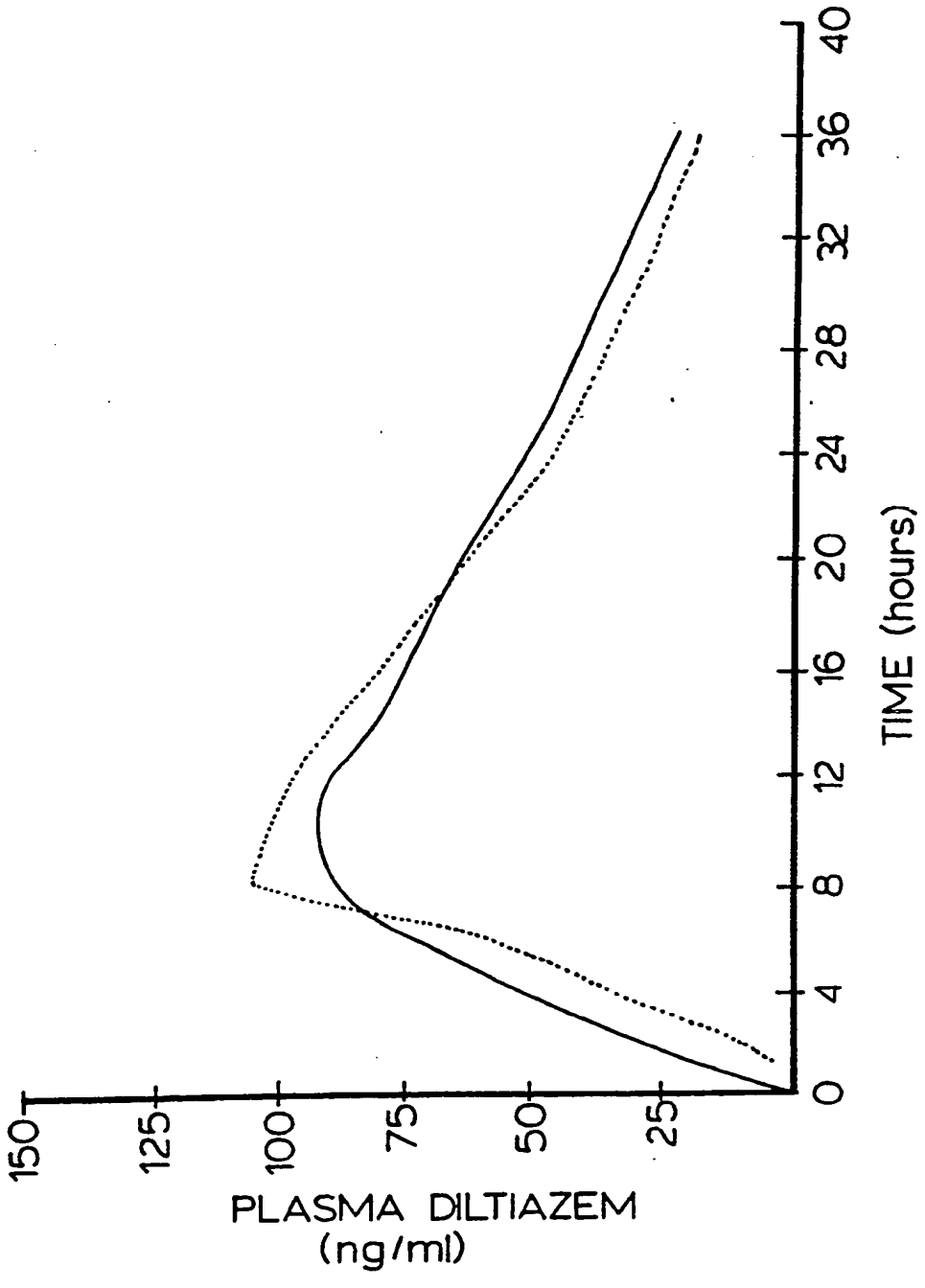

FIG. 2.

INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 92/00290

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/55 A 61 K 9/52 A 61 K 9/54

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0373417 (SCHERING) 20 June 1990, see the claims; page 3, lines 25-53; page 4, lines 21-32	1-3,12-13,16-17,20,27-28,31-32
A	EP,A,0340105 (SANOFI) 2 November 1989, see the claims; column 2, lines 9-31; column 3, lines 4-23,46-53	1-3,12-13,16-17,20,27-28,31-32
A	EP,A,0322277 (SYNTHELABO) 28 June 1989, see the claims; column 1, lines 23-52; column 2, lines 23-29	1-3,12-13,16-17,20,27-28,31-32

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° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
01-09-1992	21. 09. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0149920 (ELAN) 31 July 1985, see the claims; page 4, lines 26-35 (cited in the application)	1-4

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. CA 9200290 SA 61640

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 16/09/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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